REMARKS

Claims 1-12, 19-32, and 34-39 are pending. Claims 1-6, 8-10, 12, 20, 21, 25, and 27-32 presently stand withdrawn as being drawn to non-elected subject matter. No claim is being amended at this time; the preceding listing of claims is presented only for the convenience of the Office.

I. Independent Claims Presently Under Examination

Claim 7 as previously presented is directed to a population of **reverse-immortalised** human OEG cells, which have the ability to promote axonal regeneration from adult CNS neurons, for transplantation into a patient, and which are producible by a method that includes the steps a) through e) as recited in claim 1.

Claim 11 as previously presented is directed to a population of **reverse-immortalised** human OEG cells, which have the ability to promote axonal regeneration from adult CNS neurons, for transplantation into a patient, and which are producible by a method that includes the steps a) through e) as recited in claim 1.

Claim 19 as previously presented is directed to a **reverse-immortalised** human OEG cell, which has the ability to promote axonal regeneration from adult CNS neurons upon transplantation into a patient, produced by exposing a DNA construct within a reversibly-immortalised human OEG cell to a recombinase that excises the DNA construct by cleavage at the recombinase target sites.

Claim 22 as previously presented is directed to a **reverse-immortalised** functional human olfactory ensheathing glia (OEG) cell line, which has the ability to promote axonal regeneration from adult CNS neurons.

II. "Reverse-Immortalised" and "Reversibly-Immortalised" Cells

[A] Introduction

Certain types of cells, such as human OEG cells, can have therapeutic utility, e.g., treating neural damage in a patient. Typically, however, a large population of cells is needed to produce a therapeutically useful effect in the patient.

One strategy for generating large populations of cells is to induce the cell of interest to grow indefinitely *in vitro* (e.g., by genetically modifying the cell, e.g., by inserting an oncogene into the genetic workings of the cell). This process of inducing cells to grow indefinitely is often referred to as "immortalization."

Cells in the so-called "immortalized" state proliferate indefinitely and therefore are not typically administered to patients. This is because cells that are modified to proliferate indefinitely (e.g., modified to contain an oncogene) may also induce tumor formation in the patient. Instead, the immortalized cells are subjected to yet another genetic modification. More specifically, the genetic material in the cell that is responsible for inducing cell proliferation (previously introduced into the cell to initiate immortalization) is removed or silenced. This process of arresting cell proliferation is often referred to as "deimmortalization."

In summary, large cell populations that are potentially useful for therapy can be produced by the above described sequence of immortalization - deimmortalization. However, whether the cell population is ultimately useful depends, in very large part, on whether the cells' functional (therapeutic) properties are retained in the aftermath of two above-described genetic modifications. Further, and as will be discussed in more detail later in this Reply, whether said properties are retained by the modified cells is something that cannot be reasonably predicted in each and every case.

[B] Definitions

A reverse-immortalised cell is different from a reversibly-immortalised cell. A "reversibly-immortalised" cell is a cell that is presently in an immortalised state, but can be returned to a non-immortalised state at a later time. In contrast, a "reverse-immortalised" cell is a cell that now exists in a non-immortalised state, which is directly obtained from the "reversibly-

immortalised" cells by subjecting them to a further step of genetic modification. See also the specification at page 11, lines 6-15.

[C] The present claims

The claims as pending relate to reverse-immortalised human olfactory ensheathing glia (OEG) cells, which have the ability to promote axonal regeneration from adult CNS neurons, for transplantation into a patient, producible by the methods specified in the claims. In other words, the fact that the cells have undergone immortalisation followed by desimmortalisation has not adversely affected this capacity of the cell. The cells maintain their viability and functional properties after the excision of the immortalising transgene. Again, the inventors have found that **reverse-immortalised** OEG cells, which retain their biological function, can be produced.

III. Rejections under 35 U.S.C. § 103

[A] Claims 7, 11, and 19 stand rejected, and previously added claims 34-39 are now rejected, for allegedly being unpatentable over "Barnett *et al.* (**Brain**, 123:1581-1588, 2000, "Barnett") when taken with Salmon *et al.* (**Mol. Therapy**, 2(4): 404-414, 2000, IDS, "Salmon") in further view of Halfpenny (**The Lancet Neurology**, 1: 31-40, 2002)" (Office Action, page 5, "Halfpenny"). According to the Office Action (Page 8, bold emphasis added):

> Accordingly, in view of the combined art of Barnett and Salmon, it would have been obvious for the ordinary skilled artisan to modify the OEG cells, taught by Barnett, to produce **reversibly-immortalized** OEG cells, utilizing the methods of Salmon, with a reasonable expectation of success. One of ordinary skill in the art would be been sufficiently motivated to produce **reversibly-immortalized** OEG cells in order to produce a large number of therapeutic cells for transplantation, as suggested by Salmon (p. 404, Introduction) and further specifically suggested by Halfpenny who teach immortalized cell lines would provide sufficient numbers of cells for transplantation, which could yield large numbers of appropriate cells in homogeneity. See p. 34, col. 2, Immortalized Cell Lines.

[1] The foregoing discussion in parts **[a]** through **[c]** below are not to be construed as Applicants' solely addressing the references of record individually rather than in combination. Obviousness is a legal conclusion based on underlying findings of fact. The foregoing discussion in parts **[a]** through **[c]** below are intended to specifically address the Office's findings of fact in this case.

[a] Barnett

Barnett et al discloses that human olfactory ensheating cells (OECs) have the ability to form new myelin sheaths following transplantation into areas of persistent demyelination in the adult rat CNS [page 1585, 2nd col., 2nd paragraph]. As acknowledged by the Office, however, Barnett et al makes no mention of reverse immortalized (a requirement of the claims) cells. Further, Barnett et al also fails to teach that their cells have the ability to promote axonal regeneration from adult CNS neurons (also a requirement of the claims).

[b] Salmon

Salmon discloses methods for making *reversibly-immortalised cells* using excisable lentiviral vectors. The cell types that are reversibly immortalized in Salmon (human liver sinusoidal endothelial cells, pancreatic islet cells) are different from OEG cells. According to Salmon (page 411), "Cre-mediated excision of the proviral integrants resulted in complete growth arrest of the cells." However, Salmon does **not** teach any phenotypic or functional characteristics of these *reverse immortalised cells* (i.e., cells in which the lentivirus vector had been excised) beyond saying that these cells can survive up to 2 weeks. The disclosure is entirely silent regarding any functional biological properties of these deimmortalized cells.

With this point in mind, Applicants wish to address the following passage from the present Office Action

> Applicants' arguments regarding Salmon's teachings regarding the functionality of the resultant cells are not found to be persuasive. In fact, Salmon teaches that it is possible to produce cells that are able to survive more than two weeks in minimal culture (p. 411, col. 1, 1st ¶). Additionally, Salmon teaches that their resultant cell line exhibits the numerous phenotypic markers of the original parent cells (p. 408, col. 1, 1st ¶). Thus, Salmon provide sufficient guidance and a reasonable expectation of success that their methods would produce a cell that would maintain the characteristics of the original parental cells. It is noted that Applicants' claims read on any method of producing immortalized cells, and thus, encompass methods such as those taught by Salmon.

This portion of the rejection appears to suggest that Salmon characterised the reverse immortalised cells, i.e. cells in which the DNA construct containing the immortalising transgenes had been excised. If in fact this is the case, then Applicants respectfully disagree with the Office's characterization of Salmon. Salmon merely states on page 408, lines 9-11 that "[u]pon Cre expression, complete growth arrest is observed within 2 days and the nondividing cells survive for up to 2 weeks." Salmon does not, however, teach the phenotype or phenotypic markers of this (deimmortalized) cell line. The "resultant cell line" as referred to in the above-quoted passage from the rejection is in fact the Salmon cell line that still contains the DNA construct containing the immortalising transgenes, i.e., the cell line which resulted from reversibly immortalising hLSEC. This "resultant cell line" is referred to at page 408, lines 4-8 of Salmon (as the "resulting cell line"), and it is clear that this resultant cell line is not the reverse immortalised cell line, but the reversibly immortalised cell line.

Further, there are comments in Salmon that would lead one to reasonably conclude that not all cell types will retain their functional properties following immortalization – deimmortalization. In fact, Salmon indicates that said functional properties can be lost after the initial step of immortalization. See pages 404 and 412-413 of Salmon:

> Murine primary cells can be readily immortalized through the expression of oncogenes(1,2), although they often lose in the process part of their phenotypic characteristics. ...
>
> Because lentiviral vectors can transduce targets that are nondividing, including at least some stem cells, the protocol described here wil also permit to ask general questions about differentiation and oncogenesis. For instance, if a hematopoietic stem cell can be reversibly immortalized, does it conserve or ultimately recover its pluripotentiality?

In summary, it cannot be said that Salmon, which does not even teach that reverse immortalised hLSEC are biologically functional, provides sufficient guidance and a reasonable expectation of success that any reverse human immortalised cell would retain the characteristics of the parent cells, let alone CNS cells. All that a skilled person would learn from Salmon is that hLSEC cells can be reversibly immortalised using a lentivirus vector system. In view of this disclosure, a skilled person would not have any reasonable expectation of success that human cells, let alone CNS cells, could be reverse immortalised and retain their biological function.

[c] Halfpenny

Halfpenny et al. reviews the experimental myelin repair of different glial cells in diseases such as multiple sclerosis. However, Halfpenny et al does not consider the ability to promote axonal regeneration of these cells. In fact, according to Halfpenny et al:

> [T]he contribution of progressive axonal loss to secondary progressive multiple sclerosis mitigates against very late intervention since little can be expected of repair strategies when the axonal framework for remyelination has been lost [page 36, 2nd col., 3rd paragraph].

Therefore, in view of Halfpenny, a skilled artisan would not expect that immortalised glial cells as described in Halfpenny would be suitable to promote axonal regeneration after transplantation, as in view of the above, a skilled artisan would not have any expectation of repair or regeneration, when axonal loss already exists.

Further, Halfpenny also acknowledges that there are difficulties with producing human cells that are reversibly immortalised and are not faithful to their parent cells (see page 34, right hand column, first full paragraph and Page 34, right hand column, second full paragraph):

> Some human glia cell lines have been described, mainly derived from tumors, but they have not proved entirely faithful to their primary cell. ...
>
> Attempts have been made to immortalise human OPC, but evidence for myelin formation in vivo is lacking.

These comments demonstrate the difficulty in immortalising OPC. Halfpenny does not even go on to consider the problems involved in desimmortalisation i.e. to produce reverse immortalised human cells. In view of the difficulties, it cannot be said that one of skill in the art would have a reasonable expectation of success in generating cells as claimed. Thus, if anything, Halfpenny teaches away from the invention.

[2] Obviousness is a legal conclusion based on underlying findings of fact. The claims presently under examination are directed to populations of **reverse-immortalised** human olfactory ensheathing glia (OEG) cells. As explained above, a "reverse-immortalised" cell is a cell that now exists in a non-immortalised state, which is directly obtained from the "reversibly-immortalised" cells by subjecting them to a further step of genetic modification. The present claims also require that said cells have the ability to promote axonal regeneration from adult CNS neurons.

The Office has argued:

> [I]t would have been obvious for the ordinary skilled artisan to modify the OEG cells, taught by Barnett, to produce reversibly-immortalized OEG cells, utilizing the methods of Salmon, with a reasonable expectation of success.

However, to support such a rationale for a conclusion of obviousness, the Office must at least provide a finding that one of ordinary skill in the art would have recognized that applying the known technique (here, the methods disclosed in Salmon) would have yielded predictable results and resulted in **reverse-immortalised** human olfactory ensheathing glia (OEG) cells having the ability to promote axonal regeneration from adult CNS neurons. See MPEP § 2143.

No such finding has been made in the present rejection, nor is any such finding in the prior art of record. None of the prior art of record (alone or in combination) has shown successful reverse immortalisation of human CNS cells, let alone OEG cells. Moreover, none of the prior art has shown or suggests that the ability of OEG cells to promote axonal regeneration is conserved during the immortalisation and after the desimmortalisation process.

Salmon et al does not teach a desimmortalisation process to obtain the reverse-immortalised cells, which maintain their functional capacities. It cannot be said that Salmon, which does not even teach that reverse immortalised hLSEC are biologically functional, provides sufficient guidance and a reasonable expectation of success that any reverse human immortalised cell would retain the characteristics of the parent cells, let alone CNS cells. In fact, a fair reading of Salmon (see the passages from Salmon quoted above) would lead one to reasonably conclude otherwise. All that a skilled person would learn from Salmon is that hLSEC cells can be reversibly immortalised using a lentivirus vector system. In view of this disclosure, a skilled person would not have any reasonable expectation of success that human cells, let alone CNS cells, could be reverse immortalised and retain their biological function. A skilled person would know that the genetic manipulations the cells undergo through immortalisation and subsequent deimmortalisation could render the cells genetically unstable and result in a loss of phenotypic properties of the primary cells from which they are derived. As mentioned above, whether a specific property is retained by the modified cell is something that cannot be reasonably predicted in each and every case and for each type of cell. Therefore, it could not be expected

with a reasonable expectation of success that reverse immortalised OEG cells would be able to promote axonal regeneration from adult CNS neurons.

In view of the combined art of Barnett and Salmon, there is no reasonable expectation of success in promoting axonal regeneration using reverse-immortalised OEG of Barnett obtained through the method of immortalisation taught by Salmon. Moreover, Halfpenny would not motivate the ordinary skilled artisan to use these glial cells to promote axonal regeneration after transplantation in humans.

In view of the foregoing, it is respectfully submitted that the Office has not established a *prima facie* case of obviousness, and Applicants respectfully request that the rejection be reconsidered and withdrawn.

[B] Claim 22 stands rejected for allegedly being unpatentable over "Barnett *et al.* (**Brain**, 123:1581-1588, 2000) when taken with Salmon *et al.* (**Mol. Therapy**, 2(4): 404-414, 2000, IDS) in further view of Halfpenny (**The Lancet Neurology**, 1: 31-40, 2002)" as applied to claims 7, 11, 19, and 34-39 above and further in view of Franklin et al. (**Glia**, 17:217-224, 1996)" (Office Action, page 6).

Applicants respectfully request reconsideration and withdrawal of the rejection of claim 22 in view of the remarks below. The arguments presented above with respect to Barnett, Salmon, and Halfpenny also apply here and are incorporated by reference herein. The foregoing remarks are supplemented here to address the inclusion of the Franklin et al reference.

Franklin et al. describes the use of a retrovirus containing the temperature sensitive (ts) mutant gene of the large T antigen (Tag). In this process, the authors do not excise the oncogene after the immortalisation because they argue that the immortalising gene product is not active following transplantation into the rat [page 218, 1st col., 3rd paragraph. Material and Methods]. Nevertheless, it is explained in the present application that the continued presence of the oncogene in these cells is of concern, in as much as it may increase the risk of malignant transformation following transplantation [paragraph 0013 of the published application].

One of ordinary skill in the art would not have been motivated to obtain a clonal reverse-immortalised human OEG cell line with expectation of success and with the enough safety to

further transplantation in humans, utilizing the teachings of Franklin in combination with Barnett's, Salmon's and Halfpenny's teachings as explained above.

In view of the foregoing, Applicants respectfully request that the rejection be reconsidered and withdrawn.

The fee in the amount of $1,110 for Three Month Extension of Time is being paid concurrently herewith on the Electronic Filing System (EFS) by way of a Deposit Account authorization. Please apply any other charges or credits to deposit account 06-1050, referencing Attorney Docket No. 14829-0003US1 / PC785647US.

Respectfully submitted,

Date: October 15, 2010

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